EXHIBIT D1

COPY

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UK Intellectual Property Office
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Dear Sirs

British Patent Application No. 0606955.3
Ultizyme International Ltd.
Our Ref: JWJ01261GB

This is in response to the Examination Report dated 23 March 2007. A certified translation of the priority document, JP2003-340092, is enclosed.

Regarding novelty, it is submitted that the claims are entitled to the priority date of 30 September 2003. The Okuda and Sode (February 2004) citation, referred to in the Examination Report, is not relevant to the patentability of the claims. The Examination Report recognises that, with a valid priority claim, the claims are novel.

Regarding inventive step, the Examination Report considers that the claims are obvious in view of WO02/073181 and Oubrie *et al*. It is submitted that the claims are not obvious in view of these citations.

WO02/073181 may be considered as the closest prior art, disclosing that it is desirable to provide an oxidoreductase and an electron-transfer protein immobilised on the surface of a biosensor (see the English-language equivalent US2005/0067278). A preferred oxidoreductase is PQQGDH and a suitable electron-transfer protein is a cytochrome such as cytochrome b562. The difference between this disclosure and the subject matter of claim 1 is that the PQQGDH and cytochrome are provided as a fusion protein according to current claim 1.

WO02/073181 teaches that problems relating to enzyme electrodes have been solved by providing an electron-transfer protein and an oxidoreductase on an electrode. Figure 4 of WO02/073181 indicates that a good response is observed with a hundred fold molar excess of cyt b562, but little response is observed with a 1:1 molar ratio of GDH:CYT even in the presence of a mediator. Further, in the absence of an additional mediator no current is observed with a 1:1 molar ratio. This

teaches that a significant excess of cytochrome is required for effecting electron-transfer from GDH to cytochrome.

The requirement for an excess of cytochrome was accepted in the art prior to the present invention, but was not recognised as problematic. To exemplify this, a copy of each of Okuda *et al* (2002) and Okuda *et al* (2003) is enclosed. Both of these publications teach that a large molar excess of the cytochrome is required, and that the presence of an additional electron mediator is preferred.

Accordingly, at the priority date of the current claims, the prior art taught that a hundred-fold (or more) molar excess of cytochrome was required to effect electron-transfer from PQQGDH to cytochrome.

Surprisingly, the present inventor found that, rather than use a hundred fold molar excess of cytochrome, a fusion protein could be used to achieve electron transfer in an efficient way.

The provision of a fusion protein as defined by claim 1 is not obvious because there is no objective reason why the skilled person would expect that providing a fusion protein, which inevitably contains a 1:1 molar ratio of PQQGDH and cytochrome, would remove the requirement for an excess of cytochrome, in view of the teaching in the prior art (e.g. Figure 4 of WO02/073181) that 1:1 a ratio of proteins does not permit current to flow between the two proteins.

A fusion protein as defined by current claim 1 provides a surprising effect that cannot be predicted from the disclosure of WO02/073181. As shown in Figure 5 of the current application, the fusion protein of the invention shows a much greater response compared to co-immobilisation of PQQGDH and cytochrome b562 at a molar ratio of 1:1.

The use of a fusion protein according to the invention reduces the total amount of protein required and simplifies enzyme electrodes, providing effective electron transfer without the need for a large excess of cytochrome or an electron mediator. The present invention therefore provides a significant improvement in a GDH-based glucose sensor that could not be predicted from the prior art.

The claims should be recognised as inventive.

Yours faithfully
GILL JENNINGS & EVERY LLP

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